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Patentanmeldung Nr. Patent application No. Demande de brevet n°

99200472.1

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Sheet 2 of the certificate
Page 2 de l'attestation

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Stereocomplex hydrogels

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Title: Stereocomplex hydrogels

The present invention relates to hydrogel compositions comprised of mixtures of water soluble or water dispersible polymers in an aqueous system at least part of which polymers contain at least two groups, which groups can give an interaction. Furthermore, the present invention relates to processes for preparing such hydrogels, and the use of oligomeric or co-oligomeric groups on polymers for gel formation.

The fast developments in the field of molecular biology and biotechnology have made it possible to produce a large number of pharmaceutically interesting products in large quantities. For instance, pharmaceutically active peptides and proteins can suitably be used as drugs in the treatment of life-threatening diseases, e.g. cancer, and of several types of viral, bacterial and parasital diseases; in the treatment of e.g. diabetes; in vaccines, e.g. for prophylactic aims, and for anticonception purposes. Especially the specialized biological activities of these types of drugs provide tremendous advantages over other types of pharmaceutics.

To illustrate the fast developments, it has been reported (see e.g. Soeterboek and Verheggen, Pharm. Weekblad **130**, pp. 670-675 (1995); R.P. Evens and R.D. Sindelar, 'Biotechnology products in the pipeline', In: Pharmaceutical Biotechnology (D.J.A. Crommelin and R.D. Sindelar, eds.), Harword Academic Publishers, pp. 337-355 (1997)) that in the United States of America, about 275 biotechnological products are in phase IV studies, while more than 500 products are under investigation.

Examples of (recombinant) proteins, which are considered very interesting from a pharmacological point of view, are cytokines, such as interleukines, interferons, tumor necrosis factor (TNF), insulin, proteins for use in vaccines, and growth hormones.

Due to their nature, proteins and proteinaceous products, including peptides, which group of products will be referred to as protein drugs herein-below, cannot be administered orally. These products tend to degrade rapidly in the gastro-intestinal tract, in particular because of the acidic environment and the presence of proteolytic enzymes therein.

Moreover, to a high extent protein drugs are not able to pass endothelial and epithelial barriers, due to their size and, generally, polar character.

For these reasons, protein drugs have to be brought in the system parenterally, i.e. by injection. The pharmacokinetical profile of these products is, however, such that injection of the product *per se* requires a frequent administration. For, it is a known fact that proteinaceous material is eliminated from the blood circulation within minutes.

In other words, since protein drugs are chemically and/or physically unstable and generally have a short half-life in the human or animal body, multiple daily injections or continuous infusions are required for the protein drug to have a desired therapeutic effect. It will be evident that this is inconvenient for patients requiring these protein drugs. Furthermore, this type of application often requires hospitabilization and has logistic drawbacks.

In addition, it appears that at least for certain classes of pharmaceutical proteins, such as cytokines which are presently used in e.g. cancer treatments, the therapeutic efficacy is strongly dependent on effective delivery, e.g. intra- or peritumoral. In such cases, the protein drugs should be directed to the sites where their activity is needed during a prolonged period of time.

Hence, there is a need for delivery systems which have the capacity for controlled release. In the art, delivery systems consisting of biodegradable polymers, (e.g. poly(DL-lactide-co-glycolide), see for example: J.L. Cleland,

'Protein delivery from biodegradable microspheres', in: Protein Delivery, Physical Systems, Pharmaceutical Biotechnology, Vol. 10, (L.M. Sanders and R.W. Hendren, eds.), Plenum Press, pp. 1-39 (1997) or L. Brannon-Peppas, 'Recent advances on the use of biodegradable microparticles and nanoparticles in controlled drug delivery', Int. J. Pharm., 116, pp: 1-9 (1995)) in which matrix the proteins are present and from which they are gradually released have been proposed.

Delivery systems can be obtained by using such biodegradable polymers for example in microspheres. However, *in vitro* or *in vivo* application of such systems based on poly(lactic acid) or poly(lactic-co-glycolic acid) have some inherent drawbacks. First organic solvents have to be used to encapsulate proteins in the microspheres. Secondly, acidic products are formed during degradation, which might result in a lowering of the pH. Both a low pH and organic solvents can affect protein stability. Furthermore, it appears to be difficult to control the protein release from these systems, which can lead to a burst release.

A hydrogel system consisting of biodegradable polymers would overcome such objections. Hydrogels can be obtained by crosslinking of hydrophilic polymers. Crosslinking can be established by using aggressive and toxic cross-linking agents which are not compatible with proteins, such as bisfunctional agents, e.g., glutaraldehyde, diisocyanates and epichlorohydrin (See: Biodegradable hydrogels for drug delivery (K. Park, W.S.W. Shalaby and H.Park, eds.) Technomic Publishing Co. Inc., p. 75 (1993)). These are toxic compounds which have to be extracted from the gels before these gels can be therapeutically applied. Moreover, these compounds can also react with e.g. epsilon amine residues or lysine side chains of the protein that is present in the hydrogel matrix. This is highly unwanted because these reactions might result in loss or reduction of biological activity of the protein.

PCT/NL97/00374 describes a delivery system that provides one solution for this problem that improves the degradation properties. This hydrogel is based on biodegradable polymers. More in particular, chains of these biodegradable polymers are intermolecularly crosslinked through linking groups, and these linking groups, that keep the hydrogel together, are hydrolysable under physiological conditions, which effects the degradation of the hydrogel.

Although these hydrolysable hydrogels provide a gel with enhanced release properties, some disadvantages remain. The polymerization of dextran (-derivatives), for example, requires peroxydisulfate and TEMED as initiator/accelerator, which compounds are essentially incompatible with *in vivo* application. Furthermore, the use of an initiator may give rise to oxidation of proteins to sulfoxides. Therefore, it is required that these compounds are carefully removed.

It is the object of the present invention to provide a release delivery system that consists of a biodegradable hydrogel that can be applied *in vitro* and *in vivo* as a release system, wherein the crosslinks are not of a chemical nature, in the sense of covalent bonds. Consequently, such crosslinks do not require cleavage of chemical bonds.

To obtain a hydrogel composition that meets the demands set out in the above, several ways to modify polymeric chains have been investigated, and the present inventors have now found that when the polymer is substituted with hydrophilic grafts that contain elements with chiral differences, in particular elements that are enantiomers, a gel, i.e., a crosslinked structure, is obtained that has excellent properties, for the application as a release system, and in particular a controlled release system for example for protein drugs.

Without wishing to be limited to a certain theory, the formation of this gelled structure is believed to be caused by the interaction of the grafts, which is believed to be similar to the interaction between the constituents of so

called stereo-complexes. These stereocomplexes are racemic crystallites that are known to be formed from racemic mixtures of certain polymers. For example, it has been found (see, e.g., De Jong, et al., Macromolecules, **31**, pp. 6397-6402, (1998)) that the melting temperature of stereocomplexes of poly(lactic acid), is considerably higher than the melting temperature of both the enantiomer crystallites.

According to the present invention, the stereocomplex gel structure is the result of the interaction of oligomerized monomers of one chirality with that of oligomerized monomers of the opposite chirality, both present on hydrophilic polymers. The groups of oligomerized monomers can be present anywhere on the polymer chains, viz. also on the head or tail positions of the polymer chains. Preferably however, the groups of oligomerized monomers are present as branches or grafts on different polymer chains that constitute the gel structure.

The gel is formed by mixing at least two different systems (A) and (B), each system being a solution or a dispersion of water soluble or water dispersible polymers, which polymers have oligomeric grafts. The grafts are obtained by polymerization of preferably one type of chiral monomer (e.g. D or L lactic acid).

The hydrogel composition according to the present invention is thus comprised of a mixture of (A) a water soluble or water dispersible polymer in an aqueous system at least part of which polymer contains at least two groups, which groups are oligomers or co-oligomers at least partly formed from chiral monomers, and (B) a water soluble or water dispersible polymer in an aqueous system at least part of which polymer contains at least two groups, which groups are oligomers or co-oligomers which are at least partly formed from chiral monomers with a chirality that is opposite to that of said monomers in mixture (A), such that the chiral part of the oligomers or co-oligomers in mixture (B) are in essence complementary to that of said groups of mixture (A);

of mixtures (A) or (B) are chosen from the group comprising homo-oligomers of D-lactic acid, random co-oligomers of D-lactide/ε-caprolactone, di- and triblock blends of D-rich poly(lactic acid), poly(D-lactide-co-glycolide), di- and triblock co-oligomers of poly(ethylene glycol)/poly(D-lactic acid), poly(methyl methacrylate), poly(α-methyl-α-ethyl-β-propiolactone), poly(*tert*-butylethylene oxide), poly(*tert*-butylethylene sulfide), poly[β,-(1,1-dichloropropyl)-β-propiolactone], poly(α-benzyl glutamate), poly(methylbenzyl methacrylate), poly(vinyl-*N*-butylpyridium bromide), poly(sodium styrenesulfonate), poly(*tert*-butylthiirane), poly(α-methylbenzyl methacrylate), poly[β-(1,1-dichloroethyl)-β-propiolactone], and mixtures thereof; and said monomers of the other mixture are formed by the enantiomers of said monomers of the first mixture.

In another preferred embodiment the water soluble or water dispersible polymer of the hydrogel of the present invention is chosen from the group consisting of dextran, starch, cellulose derivates, albumin, lysozym, poly(aminoacids), poly(lysine) and related copolymers, poly(glutamic acid) and related copolymers, poly((meth)acrylates)/((meth)acrylamides), poly(vinylalchohol), poly(ethylene glycol), water soluble polyphosphazenes, or mixtures thereof.

When applied as a controlled release system, the drug to be released is incorporated after the formation of the gel, viz. after the addition of mixtures (A) and B.

Alternatively, because the gel of the present invention is prepared in the absence of organic solvents, the drug to be released can be added to the composition prior to the formation of the gel, viz. prior to the addition of system (A) and system B. The drug is thus mixed with system (A) and/or system B, which systems are subsequently mixed, upon which the gel will be formed under suitable reaction conditions.

The graft groups can be linked directly to the polymers or by means of a linking group, depending on the reactivity of the groups and the polymer. An example of such a linking group is carbonyldiimidazole (CDI). Such linking groups are converted further when the grafts are linked to the polymer. The linking group could also be applied to enhance the biodegradability of the product. According to a preferred embodiment of the present invention there is a linking group between the water soluble or water dispersible polymer and the oligomeric or co-oligomeric group, which linking group comprises a hydrolysable group.

The grafts can be formed by oligomerization of the monomers, which is preferably carried out by using an initiator. The initiator is usually incorporated in the oligomeric graft. Such initiators are compounds with a primary or secondary hydroxyl group, e.g.: lauryl alcohol, 1,4-butanediol, adipic acid, (monomethoxy)PEG, 2-(2-methoxyethoxy)ethanol, or mixtures thereof.

When an initiator is applied, the grafts in the resulting product will carry (part of) the initiator as an end group. The amount of initiator relative to the amount of graft monomers can be used to tailor the value of DP.

The oligomerization is carried out in the presence of a suitable catalyst. Such a catalyst can be chosen from the group comprising: stannous octoate, aluminum alkoxides (e.g., aluminum tris(2-propanolate), zinc powder, CaH_2, Sn(IV)tris-2-ethylhexanoate, tetraphenylporphinatoaluminum, aluminum triisopropoxide, chiral Schiff's base/aluminum alkoxides, Al(Acac), SALEN-Al-OCH_3, *t*-BuOLi, Bu_3SnOCH_3, PbO, zinc oxide, diethyl zinc, zinc chloride, stannous chloride, magnesium salt, $Zn(Acac)_2$, $ZnEt_2$-$Al(OiPr)_3$, ($ZnEt_2$ + $AlEt_3$ + nH_2O), yttrium oxide, or mixtures thereof.

The grafting of the polymers can be effected by mixing the grafts with or without the linking groups and the polymers in a suitable solvent. Preferably the grafts are mixed with the linking groups. Such solvents can be chosen

from aprotic solvents, depending on the polymer used, e.g. dimethyl sulfoxide for e.g. polydextrans, after which the grafting reaction is carried out under suitable conditions, which conditions can be easily determined by a skilled person. After this the solvent is removed.

The degree of substitution can be controlled by changing the amount of (co-)oligomeric graft and water soluble polymer, e.g. the ratio of lactides to dextran.

Another parameter that can be used in the hydrogels according to the present invention is the presence of (co-)oligomers in the hydrogel which are not grafted to the polymer. Such non-bonded (co-)oligomers form physical interaction, which interaction is similar as described in the above. The non-bonded (co-)oligomers interact with the grafts present on the polymer, thus 'occupying' the grafts and consequently reduce the interaction between the different polymer chains through the grafts, rendering a gel which is more soluble or dispersible.

Prior to mixing (A) and (B) the individual mixtures can be subjected to solvatation, which comprises mixing for a certain period of time.

An interesting possible use of the invention is the use of mixture (A) and (B) for the *in vivo* formation of the hydrogel. When mixtures (A) and (B) are mixed, the resulting mixture will initially be liquid, since the formation of a hydrogel will take some time. When this mixture is injected before the formation of a hydrogel is completed, the hydrogel will be formed *in vivo*. This is carried out by mixing *ex vivo* the mixtures (A) and (B) and injecting this mixture in liquid form after which said hydrogel forms *in vivo*.

The stereocomplex hydrogels according to the present invention, are macroscopic gels. The gels can be used in their macroscopic form, applied e.g. in implants.

Alternatively, the gels can be formed in microspheres, for example by spray drying. Another possibility for forming microspheres is described in

PCT/NL97/00625 which discloses a two phase method in which a two phase system is formed from two incompatible water soluble polymers and at least one releasable compound.

According to the present invention, a process for the preparation of a hydrogel in the form of microspheres comprises the formation of a two phase system, optionally in the presence of a releasable compound, by choosing two of said water soluble or water dispersible polymers such that they are incompatible; from which two phase system the hydrogel is formed.

Injectable microspheres, suitable for controlled release can thus be obtained.

According to the present invention, a process for the preparation of a hydrogel comprises the steps of preparing two mixtures of a substituted water soluble or water dispersible polymer, the preparation of each mixture comprising:

1) polymerization, optionally in the presence of a suitable initiator, of a monomer, where the monomer of one mixture is the enantiomer of the monomer of the other mixture.

2) reaction of the product of the previous step with a suitable coupling compound,

3) reaction of the product of the previous step with said water soluble or water dispersible polymer, and

4) mixing two said mixtures.

Preferably, the suitable initiator in step 1) contains a primary or secondary hydroxyl group.

The invention further relates to the use of two opposite enantiomeric forms of a monomer in an oligomer or co-oligomer which oligomer or co-oligomer are attached to polymeric chains to physically link these polymeric chains.

The present invention will now be illustrated in the following Examples, which are not intended to limit the scope of the invention.

Table 2: Development of storage moduli in time of dex-lactate products of Example 1 with $(DP)_{av}$ =15.

Solvatation time (h)	a[1]		b[1]		c[1]		d[1]	
	G'[2] (Pa)	G'[3] (Pa)	G'[2] (Pa)	G'[3] (Pa)	G'[2] (Pa)	G'[3] (Pa)	G'[2] (Pa)	G'[3] (Pa)
0							1972	2306
16	2402				1823	6039		
40					3453	7934		
48	2359	4911	232	302				
60	982	2383						
62	1259	4064						
68			1253	1476				
72					1721	4432		
80	1164	6717						
95			1705	1715				
96					3140	6084		
100	1553	5026						
120					2947	6639		
144							1515	1903
240					2926	8459		
264							1323	1783

[1]: **a:** Non-purified dex-lactate product containing non coupled oligomer, 1:1 Dex-(L)lactate and Dex-(D)lactate mixture (10 + 10 wt% gel). **b:** Reference; Non-purified dex-lactate product containing non coupled oligomer, Dex-(L)lactate or Dex-(D)lactate (20 wt% gel). **c:** Purified dex-lactate product, 1:1 Dex-(L)lactate and Dex-(D)lactate mixture(10 + 10 wt% gel). **d:** Reference; Purified dex-lactate product, Dex-(L)lactate or Dex-(D)lactate (20 wt% gel).

[2]: Storage moduli measured 2-3 minutes after mixing.

[3]: Storage moduli measured after gelation, viz. after 24-72 h.

Table 3: Developm nt of storage moduli in time of dex-lactate products of Example 2 with $(DP)_{av}$ =9.

Solvatation time (h)	a[1]		b[1]		c[1]		d[1]	
	G'[2] (Pa)	G'[3] (Pa)	G'[2] (Pa)	G'[3] (Pa)	G'[2] (Pa)	G'[3] (Pa)	G'[2] (Pa)	G'[3] (Pa)
0			550	727				
48					1323	3680		
60					2059	5067	529	688
156	275	1353						
180	242	1276						
252	176	1354						
276	130	1917						

[1]: **a:** Non-purified dex-lactate product containing non coupled oligomer, 1:1 Dex-(L)lactate and Dex-(D)lactate mixture (10 + 10 wt% gel). **b:** Reference; Non-purified dex-lactate product containing non coupled oligomer, Dex-(L)lactate or Dex-(D)lactate (20 wt% gel). **c:** Purified dex-lactate product, 1:1 Dex-(L)lactate and Dex-(D)lactate mixture (10 + 10 wt% gel). **d:** Reference; Purified dex-lactate product, Dex-(L)lactate or Dex-(D)lactate (20 wt% gel).

[2]: Storage moduli measured 2-3 minutes after mixing.

[3]: Storage moduli measured after gelation, viz. after 24-72 h.

The experimental data in Tables 1-3 and Figure 1 and 2 clearly demonstrate the different rheology behaviour of the hydrogels of the present invention when compared with the reference examples ('L or D' in Table 1 and experiments 'b' and 'd' in Table 2 and 3).

Moreover, the purified examples according to the present invention ('c' in Table 2 and 3) show higher storage moduli when compared with the unpurified samples according to the present invention ('a' in Table 2 and 3).

Finally, a longer solvatation time gives rise to formation of a gel with a higher final value of the modulus.

Claims

1. Hydrogel composition comprised of a mixture of
(A) a water soluble or water dispersible polymer in an aqueous system at least part of which polymer contains at least two groups, which groups are oligomers or co-oligomers at least partly formed from chiral monomers, and
(B) a water soluble or water dispersible polymer in an aqueous system at least part of which polymer contains at least two groups, which groups are oligomers or co-oligomers which are at least partly formed from chiral monomers with a chirality that is opposite to that of said monomers in mixture (A), such that the chiral part of the oligomers or co-oligomers in mixture (B) are in essence complementary to that of said groups of mixture (A);
in which hydrogel composition the groups on the polymers from mixture (A) give a physical interaction with the groups from mixture (B).

2. Hydrogel according to claim 1 in which the said oligomers or co-oligomers of mixtures (A) or (B) are chosen from the group comprising homo-oligomers of D-lactic acid, random co-oligomers of D-lactide/ε-caprolactone, di- and triblock blends of D-rich poly(lactic acid), poly(D-lactide-co-glycolide), di- and triblock co-oligomers of poly(ethylene glycol)/poly(D-lactic acid), poly(methyl methacrylate), poly(α-methyl-α-ethyl-β-propiolactone), poly(*tert*-butylethylene oxide), poly(*tert*-butylethylene sulfide), poly[β,-(1,1-dichloropropyl)-β-propiolactone], poly(α-benzyl glutamate), poly(methylbenzyl methacrylate), poly(vinyl-*N*-butylpyridium bromide), poly(sodium styrenesulfonate), poly(*tert*-butylthiirane), poly(α-methylbenzyl methacrylate), poly[β-(1,1-dichloroethyl)-β-propiolactone], and mixtures

thereof; and said monomers of the other mixture are formed by the enantiomers of said monomers of the first mixture.

3. Hydrogel composition according to claim 1 or 2 in which the water soluble or water dispersible polymer is chosen from the group consisting of dextran, starch, cellulose derivates, albumin, lysozym, poly(aminoacids), poly(lysine) and related copolymers, poly(glutamic acid) and related copolymers, poly((meth)acrylates)/((meth)acrylamides), poly(vinylalchohol), poly(ethylene glycol), water soluble polyphosphazenes, or mixtures thereof.

4. Hydrogel according to any one of the preceding claims in which there is a linking group between the water soluble or water dispersible polymer and the oligomeric or co-oligomeric group, which linking group comprises a hydrolysable group.

5. Hydrogel according to any one of the preceding claims, in which the average chain length of the oligomeric or co-oligomeric groups is sufficiently low to render the polymer soluble or dispersible in water.

6. Hydrogel composition according to any one of the preceding claims where the average degree of substitution of the water dispersible polymer with oligomeric or co-oligomeric groups is sufficiently high to obtain a network in which the crosslinks are formed by physical interaction of the water soluble or water dispersible polymers.

7. Hydrogel composition according to any one of the preceding claims where the average degree of substitution of the water soluble or water dispersible polymer with oligomeric or co-oligomeric groups is sufficiently low to render said polymer structure soluble or dispersible in water.

8. Hydrogel composition according to any one of the preceding claims in which the average degree of substitution is from 3 - 25.

9. Hydrogel composition according to any one of the preceding claims in which the oligomeric or co-oligomeric groups of one mixture comprise poly(D-lactic acid) and the oligomeric or co-oligomeric groups of the other mixture comprises poly(L-lactic acid) both with an average chain length of 7-15 monomers.

10. Hydrogel composition according to any one of the preceding claims in which all oligomeric or co-oligomeric groups have equal length.

11. Hydrogel composition according to any one of the preceding claims in which the oligomeric or co-oligomeric groups are grafts.

12. Process for the preparation of a hydrogel which comprises the steps of preparing two mixtures of a substituted water soluble or water dispersible polymer, the preparation of each mixture comprising:

1) polymerization, optionally in the presence of a suitable initiator, of a monomer, where the monomer of one mixture is the enantiomer of the monomer of the other mixture.
2) reaction of the product of the previous step with a suitable coupling compound,
3) reaction of the product of the previous step with said water soluble or water dispersible polymer, and
4) mixing two said mixtures.

13. Process according to claim 12, in which the suitable initiator contains a primary or secondary hydroxyl group.

14. Use of two opposite enantiomeric forms of a monomer in an oligomer or co-oligomer which oligomer or co-oligomer are attached to polymeric chains to physically link these polymeric chains.

15. Use of a hydrogel as defined in any of the claims 1-13 in implants.

16. Use of mixture (A) and (B) as defined in any of the claims 1-11 *ex vivo* to form a hydrogel as defined in any of the claims 1-11 *in vivo*.

17. Process for the preparation of a hydrogel as defined in any of the preceding claims 1-13 or 15-16 in the form of microspheres, which process comprises the formation of a two phase system, optionally in the presence of a releasable compound, by choosing two of said water soluble or water dispersible polymers such that they are incompatible; from which two phase system said hydrogel is formed.

18. Process for the preparation of a hydrogel as defined in any of the preceding claims 1-13 or 15-17 in the form of microspheres which comprises spray drying of at least one water soluble polymer according to any one of the preceding claims, optionally in the presence of a releasable compound.

19. Microspheres according to claim 17 or 18 which are injectable.

Title: Stereocomplex hydrogels

Abstract

The invention relates to hydrogel compositions, which can be applied as biodegradable materials and to the processes to prepare such hydrogels. The hydrogel of the present invention comprises a stereocomplex gel structure which is the result of the interaction of oligomerized monomers of one chirality with that of oligomerized monomers of the opposite chirality, both grafted to hydrophilic polymers. The grafts form an interaction which is different from a covalent chemical interaction and thus provide the gel with the required coherence.

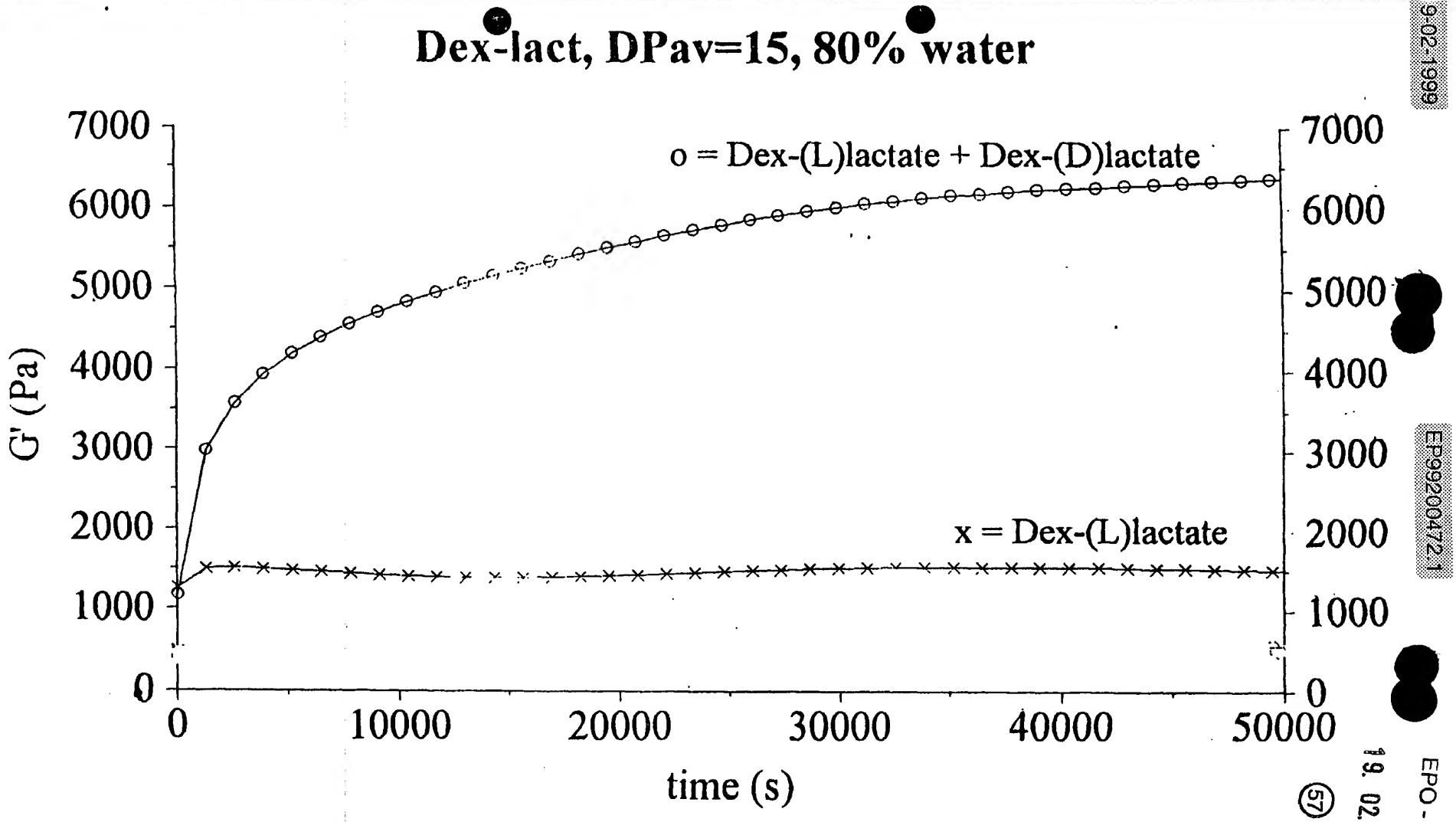

Fig. 1.

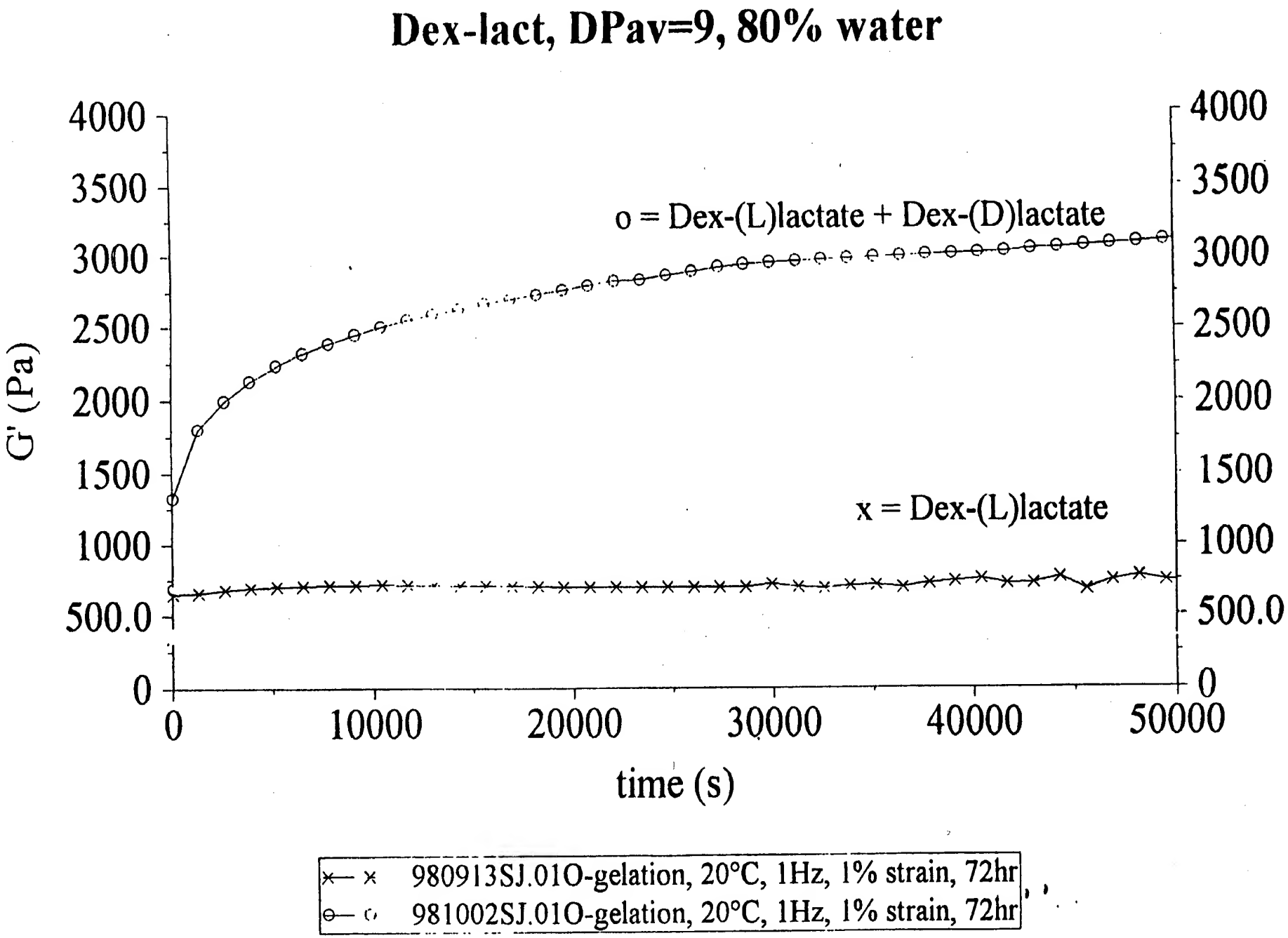

Fig. 2.